SEROTONIN AND CATECHOLAMINE METABOLISM
IN PERSONS WITH NORMAL WAKEFULNESS AND
NARCOLEPSY

A. Yu. Makarov, I. N. Ushakova,
and E. B. Loboda

Many physiological investigations have yielded evidence of the participation of biogenic mediator
amines (primarily serotonin and catecholamines) in the activity of limbico-recticular brain structures re-
sponsible for the regulation of sleep and waking. According to the results of experiments on animals, a
decrease in the serotonin concentration in the mesencephalon increases the level of wakefulness [1, 2],
whereas an increase leads correspondingly to the development of sleep [3-6]. Meanwhile an increase in
the noradrenalin concentration in the brain substance usually corresponds to a state of wakefulness, whereas
a decrease in its level accompanies a reduction in motor activity [7, 8]. The results of investigations into
the role of monoamines in the alternation of the phases of sleep are inconsistent [9-12], although on the
whole they do not contradict the concept that monoamines, especially serotonin, have a role in the regulation
of the sleep-awakening cycle under physiological conditions. These data have been generalized in several
recent surveys [13, 14].

Information on monoanaine metabolism during disturbances of wakefulness in man, manifested as
narcolepsy, is given in the literature [15-18]. However, the publications cited by no means exhaust the
problem but merely touch on some of its aspects.

The object of the present investigation was to make a detailed study of serotonin and catecholamine
metabolism in clinically healthy persons (with no disturbance of wakefulness) and in patients with hypersom-
nia of the narcolepsy type. The motivation behind the work was the need to establish objective indices for
assessing the state of neurohumoral regulation of sleep and waking under physiological and pathological
conditions in man.

EXPERIMENTAL METHOD

Altogether 45 clinically healthy persons (25 men and 20 women aged from 20 to 52 years) and 49 pa-
tients with narcolepsy (24 men and 25 women aged from 22 to 70 years) were investigated. The serotonin
concentration in the blood plasma and platelets and also in the lumbar CSF was determined flurometrically
with orthophthalic aldehyde in the writers' modification [19], and 5-hydroxyindoleacetic acid (5-HIAA) in the
CSF and urine and adrenalin, noradrenalin, dopamine, and dihydroxyphenylalanine (dopa) in the urine also
were determined fluorometrically [20, 21]. Samples of blood and CSF were taken at the same times of day
before breakfast, and samples of urine were taken from the 24-h specimen of the previous day.

EXPERIMENTAL RESULTS

Preliminary tests showed that the serotonin concentration in platelet-deprived plasma of clinically
healthy subjects with no hypersomnic disturbances averaged 0.026 ± 0.004 µg/ml. In patients with narco-
lepsy it was significantly lower, namely 0.014 ± 0.001 µg/ml (P < 0.01). These results can be compared
with information on the reduced blood serotonin concentration in healthy subjects at night [22].

Meanwhile the analysis showed that the serotonin concentration in platelet-deprived plasma did not
correlate with the intensity or frequency of the hypersomnic manifestations (Table 1). It was therefore de-
cided to investigate the serotonin concentration in the platelets, where most of it is stored, and in platelet-rich plasma, in order to determine the possibility of finding true changes in the concentration of this amine in the blood during the alternation of sleep and waking under physiological conditions and in narcolepsy.

The results showed that the platelet count in blood of patients with narcolepsy was considerably lower than in healthy subjects (Table 1). To some extent this fact could account for the low serotonin concentration in platelet-deprived plasma and the absence of any significant changes in its level in platelet-rich plasma. Meanwhile the serotonin concentrations in the platelets themselves was significantly increased (Table 1).

In the first group of patients (with frequent or very frequent imperative attacks of sleepiness combined with cataleptic states) the greatest increase ($P < 0.001$) in serotonin was observed when calculated per $10^8$ platelets (Table 1). The serotonin concentration in their platelets, contained in 1 ml plasma, also was significantly increased. By contrast, in the patients of the second group (with infrequent and not so imperative attacks of sleepiness) the serotonin concentration in the platelets showed no significant changes. Comparison of the results thus showed a lower concentration of serotonin in the platelets of subjects with less marked manifestations of the disease. Consequently, the serotonin content in the platelets is an adequate index of its blood level. Evidently in narcolepsy the blood platelets have increased ability to store serotonin.

There is evidence that the serotonin and 5-HIAA concentrations in the CSF reflect in general the state of serotonin metabolism in the CNS [23-25]. Accordingly, it was decided to study the concentrations of these substances in the CSF of nine patients with narcolepsy.

Previous investigations [25] showed that serotonin cannot be detected in the CSF of clinically healthy persons in a waking state, or its concentration is extremely low (about $0.001 \mu g/ml$). In turn, in patients with narcolepsy, the serotonin concentration in the CSF is high ($0.0119 \pm 0.0016 \mu g/ml$). The 5-HIAA concentration in the CSF is correspondingly high ($0.013 \pm 0.0023 \mu g/ml$).

The excretion of 5-HIAA in the urine of 43 patients with narcolepsy was studied. Comparison with the group of clinically healthy subjects revealed a significant ($P < 0.001$) decrease in the content of this metabolite in the 24-h specimen of urine from the patients with narcolepsy (Table 2). It depended only a little on the intensity of the principal clinical manifestations of the disease. The results are in agreement with observations by other workers [26] who found an increase in the 5-HIAA excretion of healthy subjects during waking or deprivation of sleep.

In 20 clinically healthy persons with no disturbances of wakefulness catecholamine metabolism was studied by determining the 24-hourly excretion of adrenalin, noradrenalin, dopamine, and dopa in the urine. Compared with them, a decrease in the excretion of all catecholamine fractions was found in patients with narcolepsy (Table 2). The most significant changes were observed in the excretion of dopamine and dopa ($P < 0.001$). The results are in agreement with those of other workers [15, 16, 20], who found a decrease in the concentration of adrenalin-like substances in the blood of patients with narcolepsy, and a correspondingly reduced excretion of adrenalin in the urine. The decrease discovered in the present experiments in the excretion of adrenalin precursors (dopamine and dopa) points to a decrease in the reserve capacity of the sympato-adrenal system in hypersomnia.

**DISCUSSION**

The results indicate an essential disturbance of serotonin and catecholamine metabolism in hypersomnia of the paroxysmal type. In one sense the results can be regarded as a manifestation of humoral changes taking place under physiological conditions and leading to the onset of sleep.

The changes discovered in the serotonin concentration in the body fluids during narcolepsy agree basically with the changes observed by many workers in the brain stem and hypothalamus in experiments on animals [3, 5, 6]. In this respect the increase in the serotonin and 5-HIAA concentrations in CSF is demonstrative, for it agrees with the view that an increase in the concentration of this mediator in the serotoninergic brain neurons occurs during sleep and that correlation exists between the serotonin and 5-HIAA levels in parts of the brain adjacent to the ventricular system and in the CSF [27, 28, 24].

The increase in the serotonin concentration found in the blood platelets during narcolepsy is interesting. It is particularly so in the light of existing facts [29, 30] showing the similarity between the ability of platelets and amine-containing neurons to store and liberate serotonin. The increase in the serotonin concentration in the blood platelets in hypersomnia may perhaps accompany its accumulation in serotonin-containing neurons of the brain stem, as observed in experiments during sleep. Retention of serotonin in the